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Heterogeneous Microbial Populations: using flow cytometric data for building dynamic distributed models

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Traditionally, microbial populations have been considered homogeneous in studies of fermentation processes. However, research has shown that a typical microbial population in a fermentor is heterogeneous [1-3].

Phenotypic heterogeneity arises as a result of the variability inherent to the metabolic processes within single cells. Two dominant cell variables responsible for differential gene expression are cell cycle and cell ageing [4]. Indeed, cells at different phases in the cell cycle, or with different ages, have been observed to respond differently to stress conditions [1].

Although the number of experimental methods available for single-cell analysis has boomed [5, 6], the knowledge acquired by such experimental studies has not yet been integrated into a generally accepted modeling framework able to account for distributed properties within a cell population [3].

In this work, focus was set on experimentally studying, as well as modeling, the dynamics of phenotypic heterogeneous populations of *Saccharomyces cerevisiae* during batch cultivations. Besides the common monitored variables (e.g. optical density, glucose, ethanol), single-cell total protein content and DNA content were measured by flow cytometry during the different phases of batch cultivations. Aiming at establishing a population balance model (PBM) which describes the dynamic behavior of the yeast population (including the relative contribution of different subpopulations), a systematic analysis of the flow cytometric data was performed, and mathematical descriptions for the budding initiation and cell division rates as functions of the available substrate concentration are proposed.

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